TOXICOLOGICAL REVIEW

OF

LIBBY AMPHIBOLE

In Support of Summary Information on the Integrated Risk Information System (IRIS)

November 2006

NOTICE

This document is an ***Agency Review*** **draft**. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for review of its technical accuracy and science policy implications.

U.S. Environmental Protection Agency
Region 8
Denver, CO

DISCLAIMER

This document is a preliminary draft for review purposes only and does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS—TOXICOLOGICAL REVIEW OF LIBBY AMPHIBOLE

LIST OF TABLES iv
FOREWORD v
AUTHORS, CONTRIBUTORS, AND REVIEWERS vi

1. INTRODUCTION 1

2. CHEMICAL AND PHYSICAL INFORMATION 3

3. TOXICOKINETICS 4

4. HAZARD IDENTIFICATION 6
   4.1. STUDIES IN HUMANS 6
      4.1.1. Case Reports 6
      4.1.2. Studies in Miners in Libby, Montana 6
      4.1.3. Studies in Workers in Marysville, Ohio 8
      4.1.4. Studies in Residents in Libby, Montana 13
   4.2. SYNTHESIS OF MAJOR NONCANCER EFFECTS 15
      4.2.1. Inhalation 15
      4.2.2. Mode of Action Information 17
   4.3. SUSCEPTIBLE POPULATIONS AND LIFE STAGES 18

5. DOSE-RESPONSE ASSESSMENTS 20
   5.1. INHALATION REFERENCE CONCENTRATION (RfC) 20
      5.1.1. Choice of Principal Study and Critical Effect 20
      5.1.2. Methods of Analysis 20
      5.1.3. RfC Derivation 20

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE 23

7. REFERENCES 24

APPENDIX A: SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION 27

APPENDIX B: BENCHMARK DOSE CALCULATIONS 28

LIST OF TABLES

Table 4-1 Fiber Index Values 9
Table 4-2 Range of Cumulative Fiber Exposure and Percent of Workers with Radiographic Changes by Quartile 11
Table 4-3 Range of Cumulative Fiber Exposure, Percent of Workers with Discrete Pleural Thickening, and Odds Ratios by Quartile 11
Table 4-4 Range of Cumulative Fiber Exposure and Percent of Workers with Radiographic Changes by Quartile (workers with no previous occupational exposure to asbestos) ...12
Table 4-5 Range of Cumulative Fiber Exposure, Percent of Workers with Discrete Pleural Thickening, and Odds Ratios by Quartile (workers with no previous occupational exposure to asbestos).....12

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to exposure to Libby Amphibole. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of Libby Amphibole.

In Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response,* EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing knowledge gaps, uncertainties, quality of data, and scientific controversies. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

AUTHORS, CONTRIBUTORS, AND REVIEWERS

AUTHOR
Robert Benson, Ph.D
Office of Partnerships and Regulatory Assistance
U.S. Environmental Protection Agency
Region 8
Denver, CO

REVIEWERS

This document has been peer reviewed by EPA scientists and independent scientists external to EPA. Comments from all peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. During the finalization process, the IRIS Program Director achieved common understanding of the assessment among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Economics, and Innovation; Office of Children's Health Protection; Office of Environmental Information; and EPA's regional offices.

INTERNAL EPA REVIEWERS
Region 8

James Luey, Ph.D	Mary Goldade
Aubrey Miller, MD, MPH	Wendy O'Brien, DVM, Ph.D.

Others to be added as necessary

EXTERNAL PEER REVIEWERS
Name
Affiliation

Summaries of the comments of the external peer reviewers *[and public comments, if applicable]* and the disposition of their recommendations are provided in Appendix A.

1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of Libby Amphibole and is limited to the non-cancer endpoints in the lung . The document does not contain a review of the hazard and dose-response assessment for other forms of asbestos. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and less-than-lifetime exposure durations, and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC (expressed in units of mg/m^3) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values are generally derived for chronic exposures (up to a lifetime), but may also be derived for acute ($\leq$ 24 hours), short-term (up to 30 days), and subchronic (up to 10% of average lifetime) exposure durations, all considered to be daily exposures, continuously or intermittently, throughout the duration specified. By convention in the United States, the concentration of asbestos and other asbestiform fibers in air is expressed as fibers/cubic centimeter (f/cc).

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The “oral slope factor” is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a “unit risk” is an upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water or per $\mu g/m^3$ air breathed. Second, the estimated

concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

Development of these hazard identification and dose-response assessments for Libby Amphibole has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment include the: *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006).

2. CHEMICAL AND PHYSICAL INFORMATION

Meeker et al. (2003) conducted extensive characterization of the composition and morphology of amphiboles from the Rainy Creek deposit near Libby, Montana. For the purposes of this document, this material will be called Libby Amphibole (LA). Thirty samples were collected from the site and analyzed with electron probe microanalysis using wavelength dispersive spectroscopy, X-ray diffraction analysis, and scanning electron microscopy combined with energy dispersive X-ray analysis to determine composition and morphology of both fibrous and non-fibrous amphiboles.

The amphiboles present included winchite, richterite, tremolite, and magnesioriebeckite. An evaluation of the textural characteristics showed the material to include a complete range of morphologies from prismatic crystals to asbestiform fibers. The morphology of the majority of the material is intermediate between these two varieties.

All of the amphibolites, with the possible exception of magnesioriebeckite, can occur in fibrous or asbestiform habit. These amphiboles, even when originally present as massive material, can produce abundant, extremely fine fibers by gentle abrasion or crushing of the sample. In the particles produced, the fibril diameter ranged from approximately 0.1 to 1 µm and approximately 40% of the particles are greater than 5 µm in length and have aspect ratios (length-to-width ratio) greater than 3. Therefore, with minimal disturbance, the Libby Amphibole can easily degrade into highly acicular particles that are less than 3µm in diameter and are therefore respirable.

3. TOXICOKINETICS

There are no studies on the toxicokinetics of Libby Amphibole. However, the deposition and fate of other types of inhaled asbestos fibers is largely dependent on their size and shape (ATSDR, 2001; Witschhi and Last, 1996). When asbestos fibers are inhaled, many are deposited on the epithelial surface of the respiratory tree. The location of the deposition is a function of the aerodynamic properties of the fibers. Several investigators have reviewed and investigated the factors affecting the deposition of fibers in the lungs (Myojo and Takaya, 2001; Griffis et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975). The fibers depositing in the upper airways consist primarily of relatively thick fibers (greater than about 3 µm), with thinner fibers being carried deeper into the airways and alveolar regions. All fibers with length-to-width ratios (aspect ratios) greater than approximately 3:1 and aerodynamic diameters less than approximately 2 µm meet the physical criteria necessary for deposition in the terminal bronchioles or alveoli. Fibers with aerodynamic characteristics conducive to deposition at the primary and secondary bronchioles and alveoli are considered to have greater potential to cause fibrogenesis and associated disease by either retention the alveoli or penetration into the peribronchiolar space.

Long fibers that reside in the lung may undergo a number of processes including translocation, dissolution, fragmentation, splitting, or encapsulation with protein. Asbestos fibers are not metabolized. Amphibole fibers retained in the lung do not appear to undergo any major changes. With continuing exposure of animals, amphibole levels tend to rise linearly (Wagner et al., 1974). Available data indicate slower clearance from the lung of longer chrysotile fibers or either long (>5 µm) or short amphibole fibers (Coin et al., 1994; Tossavainen et al., 1994). The increased clearance times for longer serpentine and amphibole fibers have led some investigators to conclude that longer fibers are predominant in the cause of disease despite the relatively small numbers of these longer fibers.

The principal pathway for removal of fibers from the respiratory tract is mucociliary transport. This pathway is mediated by ciliated epithelial cells that produce and move the mucous coating upwards toward the throat where it is swallowed. Additional removal of fibers is mediated by macrophages. Some fibers are not cleared from the lung, leading to an accumulation with time (Case et al., 2000; Finkelstein and Dufresne, 1999; Jones et al., 1988; Wagner et al., 1974).

Movement of fibers (translocation) within the respiratory tract may influence inflammatory reactions and cause tissue injury remote from the site of deposition. Likewise, extrapulmonary movement of fibers has been documented (Dodson et al., 2001). Translocation of fibers from the terminal bronchioles and alveoli into the transbronchiolar space, lymph nodes, and pleura of the lungs has been implicated in the cause of disease.

A quantitative assessment of exposure-response relationships for various fiber sizes and types is often difficult because of the use of monitoring techniques that did not fully characterize the distribution of fiber size and fiber chemistry. However, nearly all durable fibers with dimensional characteristics that allow penetration to the terminal bronchioles and alveoli of the lung appear to induce pathologic responses in the respiratory tract.

There is no completed pharmacokinetic model for any form of asbestos.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS

4.1.1. Case Reports

Progressive disease from exposure to Libby Amphibole was noted in a case report of fatal asbestosis in an individual 50 years after working at an offsite vermiculite processing plant for a few months at about age 17 (Wright et al., 2002). In another case report, exposures that stemmed from playing for a few years as a child in contaminated vermiculite waste materials around a former Libby vermiculite processing facility was associated with the development of asbestosis and fatal lung cancer (Srebro and Roggli, 1994).

4.1.2. Studies in Miners in Libby, Montana

4.1.2.1. Mortality Studies

Amandus and Wheeler (1987a) and McDonald et al. (1986a) studied mortality from non-malignant respiratory disease with increasing exposure to fibers among vermiculite miners at the Libby, MT mine. The Amandus and Wheeler (1987a) cohort included 575 men hired before 1970 and who were employed at the site for a least 1 year. Vital statistics as of December 31, 1981, were available for 569 workers and there were 161 deaths. The McDonald et al. (1986a) cohort included 406 men hired before January 1, 1963, and who were employed at the site for at least 1 year. Vital statistics as of July 1, 1983, were available for 397 workers and there were 165 deaths.

Amandus and Wheeler (1987a) reported the standard mortality rate (SMR) for non-malignant respiratory disease of 220.0, 170.2, 179.5, 400.7 for exposure to less than 50, 50-99, 100-399, and more than 399 fiber-years, respectively. This result was statistically significant only in the lowest exposure group ($p<0.05$) and the highest exposure group ($p<0.01$). For those workers with more than 20 years since hire, the SMR was 327.8, 283.5, 0, and 278.4 for exposure to less than 50, 50-99, 100-399, and more than 399 fiber-years, respectively. This result was statistically significant ($p<0.05$) only in the lowest exposure group.

McDonald et al. (1986a) reported standard mortality ratios (SMRs) for non-malignant respiratory disease of 3.36 (n = 7) for those with time since first employment of 10-19 years, of 5.30 (n=14) for those with time since first employment of >20 years, and of 2.55 (n = 21) for the complete cohort. Confidence limits were not reported.

A follow-up study was conducted by McDonald et al. (2004). Of the original cohort of 406 men, 165 died before July 1, 1983, and an additional 120 deaths occurred by December 31, 1998. In this study there was a statistically significant increase in mortality from non-malignant respiratory disease with increasing cumulative exposure to fibers. The exposure reconstruction was as conducted in McDonald et al. (1986a). Work histories were based on 42 defined job categories. Fibers were measure by the optical microscope technique and were obtained from company records (McDonald et al., 1986a). The overall SMR was 3.09 (95% confidence interval 2.30 to 4.06) with the relative risk of mortality increasing by 0.38 for each 100 fiber-year/ml of exposure (p = 0.0001). The adjusted relative risk for each exposure quartile is presented below.

Cumulative Exposure (fibers-yr/ml)	**Deaths observed (expected)**	**Adjusted Relative Risk (95% Confidence Interval)**
0 to <11.7	5 (3.5)	1.00
11.7 to <25.2	13 (3.7)	2.53 (0.88 to 7.24)
25.2 to <113.8	14 (3.8)	2.62 (0.93 to 8.44)
>113.8	19 (4.1)	3.11 (1.15 to 8.44)

4.1.2.2. Morbidity Studies

Two independent studies, one by researchers at McGill University (Armstrong et al., 1988; McDonald et al., 1986b) and the other by NIOSH (Amandus et al., 1987b), were conducted to determine on the prevalence of radiological changes in the lungs of workers employed in the Libby mine. Amandus et al. (1987b) evaluated the most recent x-rays taken by the company and available at the local hospital for 184 out of 191 men employed five years or more since 1975. McDonald et al. (1986b) evaluated x-rays for 244 men (164 current employees and 80 former employees living within 200 miles of the mine) who were examined on July 1, 1983, using a standardized technique. All x-rays for both studies were read by three experienced readers using ILO (1980) classification.

Armstrong et al. (1988) provided a summary table of the McGill and NIOSH studies showing the prevalence of radiographic changes of both studies. In both studies

the prevalence of both small opacities and pleural thickening (including both discrete and diffuse pleural findings) of the chest wall was srongly associated with fiber-years of exposure. Both studies found small opacities to be independently related to age, smoking, and fiber-years of exposure. After controlling for smoking and age, the relationship between pleural changes and fiber-years of exposure reached statistical significance only in the McGill study.

McGill Study				
Exposure Group (f-year)	**n**	**Small opacities*** **%**	**Pleural thickening**** **%**	**Pleural calcification** **%**
<15	119	10.1	19.3	7.6
15 to <30	37	18.9	16.2	8.1
30 to <85	51	17.6	43.1	19.6
>85	37	45.9	45.9	18.9
All	244	18.4	27.9	11.9

NIOSH Study				
Exposure Group (f-year)	**n**	**Small opacities*** **%**	**Pleural thickening**** **%**	**Pleural calcification** **%**
<15	63	0.0	6.3	1.6
15 to <30	29	3.4	3.4	0.0
30 to <85	44	6.8	13.6	6.8
>85	48	29.2	27.1	6.3
All	184	9.8	13.0	3.8

* Profusion greater than or equal to ILO category 1/0

** Includes unilateral or bilateral discrete pleural thickening (pleural plaques) or diffuse pleural thickening on the chest wall

4.1.3. Studies in Workers in Marysville, Ohio

Lockey et al. (1984) conducted a study of respiratory disease in workers employed in a facility that used vermiculate ore from Libby, Montana. The ore was used in the manufacturing facility from 1957 to 1980.

Industrial hygiene sampling for airborne fibers using membrane filters at a sampling rate of 2 L/min was initiated in the facility in 1972. Before 1976 sampling was accomplished by industrial hygiene personnel following an employee with a sampling device. After 1976 fiber levels were measured by industrial breathing zone sampling.

Exposure indexes expressed as fibers/cc were developed for each department in the facility, based on an 8 hour time-weighted average (Table 4-1). There was a substantial reduction in airborne fiber levels after the implementation of improved environmental controls in 1973 to 1974. Therefore, a separate index was developed before and up through 1973 and for the period beginning with and continuing after 1974. The industrial hygiene values used to estimate the ≤1973 exposure index per department were mean fiber values for the year ≤1973 or the mean fiber values from the year industrial hygiene values were first available. The ≥1974 exposure index was developed in a similar manner. The authors stated that the ≤1973 exposure index most likely underestimates prior employee exposure to fibers.

Collected fibers were analyzed by polarized light microscopy with dispersion staining. Additionally, fiber analysis was done by scanning electron microscopy with energy dispersive X-ray analysis and transmission electron microscopy with selected area electron diffraction. Particles with a length greater than 5 µm, a diameter less than 3 µm, and an aspect ratio of 3:1 or greater were counted as fibers.

Table 4-1: Fibers Index Values

Work Area	**fibers/cc <= 1973**	**fibers/cc >1973**
Trionizing	1.511	0.375
Control Area	0.049	0.049
Polyform	0.049	0.049
Packaging	0.25	0.031
Warehouse	0.11	0.11
Plant Maintenance	1.264	0.212
Research	0.049	0.049
Office	0.049	0.049
Other	0.049	0.049
Pilot Plant	1.264	0.212
Central Maintenance	0.415	0.131

Workers (n = 512, 480 males and 32 females, with a median age of 37.5 years, and median duration of employment of 10 years) were surveyed for the presence of respiratory symptoms by questionnaire and for pneumoconiosis by chest radiograph. Pulmonary function was measured by spirometry and single-breath carbon monoxide diffusing capacity. Cumulative fiber exposure indexes, expressed as fibers-yr/cc, were derived for each worker from available industrial hygiene data and work histories (Lockey, 1985). The estimated cumulative exposure for the work force ranged from 0.01 to 39 fibers-yr/cc.

Discriminate analysis demonstrated significant correlates with shortness of breath and pleuritic chest pain to cumulative fiber exposure. The radiographic changes were limited to pleural changes and involved 4.4% of the workers. Parametric and discriminate analysis demonstrated a significant correlation with radiographic changes and cumulative fiber exposure. There were no correlations between spirometry or single-breath carbon monoxide diffusing capacity and cumulative fiber exposure.

The authors concluded that exposure to vermiculite contaminated with LA can cause pleural changes in exposed workers. The authors stated that this conclusion is supported by the previously identified 12 cases of benign pleural effusions in this working population and the association of pleural radiographic changes and pleuritic chest symptoms with cumulative fiber exposure. The authors speculated that the lack of significant parenchymal radiographic changes, of spirometric effects, and of changes in carbon monoxide diffusing capacity most likely reflected the low cumulative exposure to fibers.

The University of Cincinnati research team conducted a follow-up study of the same workers (Lockey et al., 2006). There was no exposure to LA or other source of asbestos in the manufacturing facility after 1980. The subjects in this study (n = 280) included all living workers from the manufacturing facility who participated in the earlier study. The methodology used in the follow-up study was similar to that used in Lockey et al. (1984). The evaluation of each worker included an interview to determine work and health history, spirometry, brief pulmonary examination, and chest X-ray. Exposure was quantified using the procedure previously defined (Lockey, 1985) and the data on fiber levels in Table 4-1. Each worker supplied a detailed work history (start and end date for each area within the facility). The exposure reconstruction quantified cumulative exposure for each individual and took into account that an individual could have been exposed at multiple areas within the facility. The estimated cumulative exposure for this follow-up study ranged from 0.00778 to 28.1 fibers-yr/cc.

Radiographic images were analyzed using International Labour Organization criteria (ILO, 2000). Discrete pleural thickening is defined as pleural thickening with or without calcification along the chest wall, diaphragm and/or pericardium, excluding solitary costophrenic angle blunting. Diffuse pleural thickening is defined as pleural thickening, including costophrenic angle bunting, with or without calcification. A

parenchymal (interstitial) change is defined as irregular opacity with profusion >1/0. Radiographic changes found in the study population are summarized in Tables 4-2 to 4-5.

Table 4-2: Range of Cumulative Fiber Exposure and Percent of Workers with Radiographic Changes by Quartile

Exposure Quartile	**Range of Exposure (fiber-year/cc)**	**Number of Workers**	**Discrete Pleural Thickening**** (n)*	**Diffuse Pleural Thickening**** (n)	**Parenchymal Change**** (n)
1st	0.00778-0.28	70	7.1% (5)	0	0
2nd	0.29-0.95	70	20.0% (14)	0	0
3rd	0.96-2.42	70	31.4% (22)	1.4% (1)	1.4% (1)
4th	2.42-28.10	70	32.9% (23)	15.7% (11)	10.0% (7)
Total		280	22.9% (64)	4.3% (12)	2.9% (8)

* Significant trend p< 0.01

** The column for **Discrete Pleural Thickening** contains individuals with that diagnosis only. Two subjects are included in both the **Diffuse Pleural Thickening** and **Parenchymal Change** columns as each was diagnosed with both conditions. The cumulative exposures for these two subjects are 2.33 fibers-year/cc and 17.20 fibers-year/cc-year.

Table 4-3: Range of Cumulative Fiber Exposure, Percent of Workers with Discrete Pleural Thickening, and Odds Ratios by Quartile

Exposure Quartile	**Range of Exposure (fiber-year/cc)**	**Number of Workers**	**Discrete Pleural Thickening** (n)*	**Crude Odds Ratio**	**95% CI**
1st	0.00778-0.28	70	7.1% (5)	Reference	---
2nd	0.29-0.95	70	20.0% (14)	3.25	1.10, 9.59
3rd	0.96-2.42	70	31.4% (22)	5.96	2.11, 16.86
4th	2.42-28.10	70	32.9% (23)	6.36	2.25, 17.95
Total		280	22.9% (64)		

*Significant trend p< 0.01

Table 4-4: Range of Cumulative Fiber and Percent of Workers with Radiographic Changes by Quartile (workers with no previous occupational exposure to asbestos)

Exposure Quartile	Range of Exposure (fiber-year/cc)	Number of Workers	Discrete Pleural Thickening** (n)*	Diffuse Pleural Thickening** (n)	Parenchymal Change** (n)
1st	0.00778-0.28	63	6.4% (4)	0	0
2nd	0.29-0.96	63	15.9% (10)	0	0
3rd	0.97-2.42	63	34.9% (22)	1.6% (1)	1.6% (1)
4th	2.43-28.10	63	31.8% (20)	14.3% (9)	9.5% (6)
Total		252	22.2% (56)	4.0% (10)	2.8% (7)

* Significant trend p< 0.01

** The column for **Discrete Pleural Thickening** contains individuals with that diagnosis only. Two subjects are included in both the **Diffuse Pleural Thickening** and **Parenchymal Change** columns as each was diagnosed with both conditions. The cumulative exposures for these two subjects are 2.33 fibers-year/cc and 17.20 fibers-year/cc.

Table 4-5: Range of Cumulative Fiber Exposure, Percent of Workers with Discrete Pleural Thickening, and Odds Ratios by Quartile (workers with no previous occupational exposure to asbestos)

Exposure Quartile	Range of Exposure (fiber-year/cc)	Number of Workers	Discrete Pleural Thickening (n)*	Crude Odds Ratio	95% CI
1st	0.00778-0.28	63	6.4% (4)	Reference	---
2nd	0.29-0.96	63	15.9% (10)	2.78	0.82, 9.40
3rd	0.97-2.42	63	34.9% (22)	7.92	2.54, 24.68
4th	2.43-28.10	63	31.8% (20)	6.86	2.19, 21.52
Total		252	22.2% (56)		

* Significant trend p< 0.01

This study again demonstrates that exposure to LA can cause radiographically evident pleural changes in exposed workers. Although there was no additional exposure to LA after 1980, the incidence of adverse effect radiographic changes in the lungs increased from 4.4% to 29.3% (82/280, including discrete and diffuse pleural thickening and parenchymal change) compared to the initial study. The follow-up study also shows a clear exposure-response relationship and a progression to more extensive damage (that is, diffuse pleural thickening and parenchymal change) to the lung with increasing cumulative exposure to LA.

Lockey et al. (2006) does not have an unexposed group as a control. All individuals in the study had some exposure to LA in the facility. It is difficult to compare the prevalence of pleural radiographic abnormalities across study cohorts due to the latency between exposure and response, variation in demographics, variation in radiographic film techniques, and inter-reader variability. However, studies in the US among individuals with no reported exposure to asbestos have found a low prevalence of pleural radiographic abnormalities. Castellan et al. (1985) conducted a study in employees working in environments free from exposure to respiratory hazards using chest radiography and a standard occupational history questionnaire. Workers who had worked for a total of 5 years or more in previous jobs with possible hazardous respiratory exposure were excluded from the study. Chest radiograms were available for 1,422 individuals, including 50.6% males, 49.4% females, 52.5% whites, 44.2% blacks, 47.0% current smokers, and 38.5% nonsmokers. The mean age was 33.8 years, with a range from 16 to 70 years. Small opacities of profusion greater than or equal to 1/0 were identified in only 3 (0.2%) of the radiographs and these were unilateral and uncalcified in all cases.

Anderson et al. (1979) also reported on the incidence of radiographic anomalies in an unexposed population of residents from urban New Jersey. Of radiographs from 326 individuals with no known personal occupational contact with asbestos, they report 2 (0.6%) with pleural plaques and 4 (1.2%) with pleural thickening.

4.1.4. Studies in Residents in Libby, Montana

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a Health Consultation in Libby. The mortality study found markedly elevated death rates from asbestosis, lung cancer, and mesothelioma for the period of 1979-1998. Mortality from asbestosis was approximately 40 times higher than the rest of Montana and 60 times higher than the rest of the United States (ATSDR, 2002a, 2000). ATSDR also documented asbestos-related pleural disease in a case-series involving a small group of residents with no history of occupational exposure to asbestos (ATSDR, 2002b).

Peipins et al. (2003) conducted a cross-sectional interview and medical testing in Libby, Montana. The objective was to identify and to quantify asbestos-related radiographic abnormalities among persons exposed to vermiculite in Libby and to examine associations between the radiographic outcomes and participant's self-reported

exposure. The program was conduced from July through November 2000 and from July through September 2001. The study included chest radiograms in 6,668 individuals over 18 years of age who had lived, worked, or played in Libby for at least 6 months before December 31, 1990. The study found pleural abnormalities in 17.8% and interstitial abnormalities in <1% of the participants. The majority of these individuals (>70%) did not directly work for the mine or with any secondary contractors for the mine. Although no quantitative exposure analysis was conducted, the prevalence of pleural abnormalities increased with increasing number of self-reported exposure pathways. The factors most strongly associated with pleural abnormalities were being a former employee of W. R. Grace, being older, having been a household contact of a former employee of W. R. Grace, and being a male. Environmental exposures and other non-occupational risk factors were also important predictors of radiographic abnormalities. Although no quantitative exposure analysis was conducted, a statistically significant trend of increasing prevalence of pleural abnormalities was found associated with increasing number of self-reported exposure pathways. The odds ratios ranged from 1.4 for one pathway to 3.75 for equal to or more than 12 pathways. The relationship between increasing pleural abnormalities with increasing number of exposure pathways was apparent even after removal of former W. R. Grace employees from the analysis.

A follow-up to this study used high-resolution computed tomography (HCRT) to further assess the presence of pulmonary abnormalities (Muravov et al., 2005). Of 353 participants whose previous chest radiographs were classified as indeterminate for pleural abnormalities (that is, only one of the three B-readers noted an abnormality, and thus not considered to be a case) in Peipins et al. (2003), 98 (27.8%) individuals were identified with pulmonary abnormalities using HCRT. Of these 98 individuals, 69 (70.4%) were either former vermiculite mine/mill workers or household contacts, and 40 (40.8%) showed pleural calcification on HRCT. Thirty out of the 40 individuals with pleural calcification reported having no occupational exposure to either Libby vermiculite or asbestos.

Whitehouse (2004) evaluated patients from Libby seen in his pulmonary medicine practice for progressive loss of pulmonary function in relation to their radiologic findings. For this study records of 123 individuals were evaluated. Of these 123 individuals, 79% were former employees of W. R. Grace, 22% were household contacts of former employees, and 8% had environmental exposure only. Of the 123 individuals evaluated, 94 demonstrated average age-corrected accelerated loss per year of vital

capacity at 3.2%, total lung capacity at 2.3%, and single breath carbon monoxide diffusion (DLCO) at 3.3%. All 123 of the participants had pleural changes with minimal to no interstitial disease. No exposure information was reported.

Two studies have been conducted on auto-immune responses in residents of Libby (Noonan et al., 2006; Pfau et al., 2005). These studies support the hypothesis that auto-immunity plays a role in the progression of asbestos-related lung disease.

As part of the multifaceted assessment of exposure to asbestos in the community, Pfau et al. (2005) tested age- and sex-matched sets of 50 serum samples from Libby and another community in Montana with no exposure to asbestos for nuclear antigens (ANA assay) on HEp-2 cells using indirect immunofluorescence intensity, for the concentration of serum immunoglobulin A (IgA), for rheumatoid factor titer, and for antibodies to extractable nuclear antigen (ENA). The individuals from Libby who participated in the study were scored for severity of asbestos-related lung disease (none, limited, moderate, or severe) and asbestos exposure score (none, minimal, low, moderate, or high). The samples from the Libby residents showed significantly higher frequency of positive ANA and ENA tests, increased mean fluorescence intensities of titers of the ANAs, and higher serum IgA. There were also positive correlations between ANA titers and both lung disease severity score and extent of exposure score.

Noonan et al. (2006) conducted a nested case-control study of systemic autoimmune disease (systemic lupus erythematosus, scleroderma, or rheumatoid arthritis) among a cohort of 7,307 current and former residents of Libby, Montana. The odds ratios and 95% confidence limits for systemic autoimmune disease among those ≥ 65 years of age who had worked for the mining company were 2.14 (0.90-5.10) for all systemic autoimmune diseases and 3.23 (1.31-7.96) for rheumatoid arthritis. Exposure to asbestos while in the military was also an independent risk factor in this age group.

4.2. SYNTHESIS AND EVALUATION OF MAJOR NON-CANCER EFFECTS

4.2.1. Inhalation

Exposure to asbestos fibers through inhalation is associated with noncancer diseases of both the pleural and interstitial lung tissue. The American Thoracic Society (ATS, 2004) defines nonmalignant asbestos-related disease to include the conditions of

interstitial pulmonary fibrosis (asbestosis), benign (nonmalignant) pleural effusions, discrete pleural fibrosis (pleural plaques), diffuse pleural fibrosis, and obstruction of pulmonary airflow. Rounded atelectasis, which is a benign form of subpleural lung collapse, has also been associated with asbestos exposure (Terra-Filho et al. 2003). Asbestos diseases are generally dose dependent and have latency periods ranging from a year to several decades, depending on the health endpoint of concern. The latency varies for nonmalignant effects, from approximately a year for pleural effusion to several years for asbestosis (Cugell and Kamp, 2004). Once established, asbestos-related nonmalignant interstitial and pleural disorders may remain static or progress in severity in the absence of continued exposure, but they rarely regress (Becklake, 1994). For example, the American Thoracic Society concluded that: 1) slow progression of asbestos-related pleural disease is typical, with up to 85% of heavily exposed workers and 17% of environmentally exposed populations showing progression of their disease over time, 2) the presence of asbestos-related pleural disease has been associated with a greater risk of mesothelioma and lung cancer compared with subjects of comparable histories of asbestos exposures who do not have such abnormalities, and 3) epidemiologic studies have shown a significant reduction in lung function attributable to both discrete and diffuse pleural fibrosis, even in the absence of radiological evidence of interstitial fibrosis (asbestosis) (ATS 2004). Furthermore, the presence of bilateral pleural disease (discrete or diffuse) is a strong marker of asbestos exposure, reaching a predictive value of 81% after ruling out other potential etiologies (Rosenstock and Hudson, 1987). In particular, findings of discrete pleural fibrosis are highly specific for asbestos exposure and occur only rarely in individuals without a history of exposure to asbestos (Cotran et al., 1999) as indicated by the low prevalence in unexposed U.S. populations (Castellan et al., 1985; Anderson et al., 1979).

The studies summarized in section 4.1 have documented an increase in mortality and in radiographic changes in the lungs among employees of the Libby, Montana vermiculite mine (Amandus et al., 1987a, b, c; Armstrong et al., 1988; McDonald et al., 2004, 1986a, b; Peipins et al., 2003). Additional studies (Lockey et al., 2006, 1984) have documented an increase in radiographic changes in the lungs among employees of a manufacturing facility that used Libby Amphibole. Finally, additional studies have documented an increase in radiographic changes in lung (Peipins et al., 2003) and progressive loss on lung function (Whitehouse, 2004) among residents of Libby, Montana. Two studies (Pfau et al, 2005; Noonan et al., 2006) also reported an increase in autoimmune responses among residents of Libby, Montana.

While several of the studies discussed above lack quantitative exposure-response data, the data collected by Lockey et al. (2006, 1984) provide detailed exposure reconstructions for every individual in the study using reported work histories and measured concentrations of Libby Amphibole in the breathing zone for each area in the manufacturing facility. Lockey et al. (1984) and Lockey et al. (2006), a follow-up to the 1984 study using the same population of exposed workers still living, show that exposure to LA causes adverse effects (discrete pleural thickening, diffuse pleural thickening, and/or parenchymal changes) in the lung using internationally recognized diagnostic criteria. The increase in incidence of adverse effects is positively associated with an increase in cumulative exposure to LA. When the results of Lockey et al. (2006) are compared to the results of Lockey et al. (1984), there is a substantial increase in the incidence of adverse effects even in the absence of additional exposure to LA. No exposure to LA occurred after 1980 in the manufacturing facility. This result demonstrates that an adverse effect could manifest itself from even short term exposure to LA if the threshold for toxicity (duration x concentration) is exceeded and sufficient time has elapsed after exposure to allow the structural changes in the lung to occur and be visible with standard chest radiography.

4.2.2. Mode-of-Action Information

The precise mechanisms causing toxicity injury from exposure to asbestos have not been established. However, nearly all durable fibers with dimensional characteristics that allow penetration to the terminal bronchioles and alveoli of the lung appear to induce pathologic response in the respiratory tract (ATSDR, 2001; Witschi and Last, 1996).

Asbestos causes several forms of lung disease in humans: asbestosis (interstitial pulmonary fibrosis), discrete pleural fibrosis (pleural plaques), diffuse pleural fibrosis, pleural effusions, lung cancer, and malignant mesothelioma. Asbestosis is characterized by a diffuse increase of collagen in the alveolar walls (fibrosis) and the presence of asbestos fibers, either free or coated with a proteinaceous material (asbestos bodies). Discrete pleural fibrosis (pleural plaques) are discrete areas of white or yellow thickening of the parietal pleura. The fibrosis is usually situated on the chest wall but can also occur on the diaphragm, pericardium, and mediastinum (Rudd, 1996). The costophrenic angles and apices of the thoracic cavity are generally spared (ATS, 2004). Discrete pleural fibrosis typically does not appear until 20 to 30 years after exposure to asbestos

(Hillerdal, 1994). Diffuse pleural fibrosis results from thickening and fibrosis of the visceral pleura with fusion to parietal pleura over a wide area (Solomon, 1991). This condition affects visceral pleura and is very different in appearance from discrete pleural fibrosis observed on the parietal pleura. Diffuse pleural fibrosis is less specific to asbestos exposure than discrete pleural fibrosis because many other nonasbestos-related exudative pleural effusions can result in the development of diffuse pleural fibrosis. Malignant mesothelioma is a tumor of the cells covering the surface of the visceral and parietal pleura.

The physical-chemical attributes of the fiber are important in determining the type of toxicity observed. Fiber dimension (width and length) and other characteristics such as chemical composition, surface area, solubility in physiological fluids, durability, surface charge (zeta potential), and surface reactivity may all play important roles in both the type of toxicity observed and the biologically significant dose. Data indicate that both direct interaction between fibers and cellular components and cell-mediated processes may be involved.

After the fibers are deposited in the lung, they may be taken up by alveolar macrophages. Once engulfed by the macrophage, small fibers may remain in place or be removed across the bronchiole or alveolar membrane and transported to the interstitial and pleural space. Longer fibers that are not easily engulfed by the macrophages may remain in the alveoli for extended periods of time. It is believed that macrophages release mediators (lymphokines and growth factors) that attract immunocompetent cells or stimulate collagen production. Thus the mediators of the lung disease may be the inflammatory response or the initiation and promotion of the carcinogenic process.

It is known that superoxide dismutase or free radical scavengers added to in vitro systems protect cells from asbestos related cell injury. This observation suggests that the generation of active oxygen species and lipid peroxidation may be involved in the mechanism of action. This mechanism could be mediated by the interaction of iron with oxygen on the surface of the fiber to produce hydrogen peroxide and hydroxyl radicals.

4.3. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

There are no data for LA on susceptible populations or life stages. The occupational studies on LA were conducted in adults healthy enough for full time

employment. The studies on residents in Libby, Montana, involved environmental exposure to the entire population. One study on the prevalence of mesothelioma following environmental exposure to crocidolite indicated that exposure during childhood did not appear to increase susceptibility to later disease (Hansen et al., 1998).

5. DOSE RESPONSE ASSESSMENT

5.1. INHALATION REFERENCE CONCENTRATION (RfC)

5.1.1. Choice of Principal Study and Critical Effect

The principal study is Lockey et al. (2006), an occupational study in humans exposed to LA. This study was conducted in a large population of workers (n = 252). The research team did a very thorough analysis of exposure from the employment history of each worker and used the best available industrial hygiene data on the concentration of LA in the breathing zone in the various work areas in the facility.

The critical effect is discrete pleural thickening. This is an adverse effect recognized by the American Thoracic Society (ATS, 2004) and occurs first in the continuum of effects attributed to exposure to LA.

5.1.2. Methods of Analysis

EPA used benchmark dose methodology (EPA, 2000, 1995) in its analysis of the data from Lockey et al. (2006). The dose metrics evaluated were both cumulative exposure (fibers-yr/cc) and concentration (fibers/cc). To avoid any bias from non-quantified previous exposure to asbestos, EPA used only the data from workers who reported no previous exposure to asbestos. See Appendix B for the details of the analysis.

5.1.3. RfC Derivation

5.1.3.1. *Point of Departure*

The point of departure is based on the upper 95% confidence limit of the concentration showing a 5% prevalence of pleural radiographic changes ($BMCL_{05}$) from the study in humans exposed to LA. The $BMCL_{05}$ was used because this is a large study (n = 252, with no previous occupational exposure to asbestos), such findings are highly specific to exposure to asbestos, and the background incidence of comparable radiographic abnormalities in un-exposed individuals in the human population is low (Castellan et al., 1985; Anderson et al., 1979). The $BMCL_{05}$ was adjusted to continuous

exposure. The point of departure for cumulative continuous exposure is 0.04 fibers-yr/cc. See Appendix B for details of the benchmark dose and other calculations.

For some applications it is more useful to have the RfC expressed in concentration units only (fibers/cc). The point of departure in concentration units only for continuous exposure is 0.004 fibers/cc. See Appendix B for details of the benchmark dose and other calculations for this value.

5.1.3.2. *Uncertainty Factors*

Total Uncertainty Factor. The total factor of 10 is used to develop the reference concentration. Each individual factor is discussed below.

Interspecies. An interspecies factor is not used because the RfC is based on a study in humans.

Intraspecies. A ten-fold uncertainty factor is used for intraspecies extrapolation as there are no data to justify departure from the default value. Only individuals healthy enough for full time employment were included in the study.

LOAEL to NOAEL. A LOAEL to NOAEL extrapolation is not needed as a benchmark dose analysis was conducted. See Appendix B.

Subchronic to Chronic Exposure. As the exposure in the facility was long term (from approximately 9 weeks to more than 23 years, with approximately 70% of the workers having a duration of exposure of more than 6 years), a subchronic to chronic uncertainty factor is not needed.

Data Base. A data base uncertainty factor is not used. Although there are no data in laboratory animals or humans on general systemic effects, developmental and reproductive effects, neurotoxicity, or developmental neurotoxicity, it is generally acknowledged that the adverse effects of exposure to asbestos include radiographic changes in the lung (ATSDR, 2001). Therefore, for the purposes of developing the RfC for LA, the data base is considered complete and no uncertainty factor is applied. The human study was conducted in a large population of workers (n = 252, with no previous occupational exposure to asbestos) with a large range in duration of exposure (from approximately 9 weeks to more than 23 years). The study was conducted over 20 years after the facility stopped using vermiculate ore from Libby, Montana, allowing adequate time to observe any latent pleural abnormalities on chest radiography. As in all epidemiological studies, there is some uncertainty in the exposure reconstruction. This uncertainty, however, does not require the application of an additional uncertainty factor.

5.1.3.3. *RfC*

The RfC based on cumulative exposure is 0.004 fibers-year/cc (0.04 divided by a total uncertainty factor of 10, see 5.1.3.1 and 5.1.3.2). This value can be used to calculate a hazard index for a scenario that includes duration and concentration dependent exposure to LA. This value can be used for any duration of exposure (acute to chronic). However, it should not be used for acute and short term exposure if additional future exposure is anticipated.

The RfC based on concentration only is 0.0004 fibers/cc (0.004 divided by a total uncertainty factor of 10, see 5.1.3.1 and 5.1.3.2). This value applies to subchronic and chronic exposure.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

Libby Amphibole has been shown to cause discrete pleural thickening, diffuse pleural thickening, and parenchymal changes in a population of workers exposed in a manufacturing facility (Lockey et al., 2006). The study documenting these effects established a robust exposure-response relationship. These results are consistent with numerous other studies in occupational and residential populations. The principal study for the derivation of the RfC for Libby Amphibole is Lockey et al. (2006). The critical effect is discrete pleural thickening with a $BMDL_{05}$ of 0.04 fibers-yr/cc (cumulative exposure) or 0.004 fibers/cc (concentration only) in the population with no previous occupational exposure to asbestos. The total uncertainty factor is 10 for inter-human variability.

The RfC based on cumulative exposure is 0.004 fibers-yr/cc. This value can be used to calculate a hazard index for a scenario that includes duration and concentration dependent exposure to LA. This value can be used for any duration of exposure (acute to chronic). However, it should not be used for acute and short term exposure if additional future exposure is anticipated.

The RfC based on concentration only is 0.0004 fibers/cc. This value applies to subchronic and chronic exposure.

These RfC's both merit a high confidence rating. The principal study was conducted in a large population (n = 280) exposed to LA with no exposure after 1980. The exposure response relationship was derived only for the population who reported no previous occupational exposure to asbestos (n = 252). It is well documented in the scientific literature that the lung is the only significant target tissue for toxicity following inhalation of asbestos and other asbestiform fibers. Thus, the lack of studies for systemic toxicity, reproductive and developmental toxicity, neurotoxicity, and developmental neurotoxicity is not considered a data base deficiency.

7. REFERENCES

Amandus, HE; and Wheeler, R (1987a) The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. Amer J Ind Med 11:15-26.

Amandus, HE; Althouse, R; Morgan, WKC; et al. (1987b) The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part III. Radiographic findings. Amer J Ind Med 11:27-37.

American Thoracic Society (ATS) (2004) Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 170:691-715.

Armstrong, BG; McDonald, JC; Sebastien, P; et al. (1988) Radiological changes in vermiculite workers exposed to tremolite. Ann Occup Hyg 32:469-474.

ATSDR (2000) Health Consultation: mortality from asbestosis in Libby, Montana. Atlanta, GA: Agency for Toxic Substances and Disease Registry. Available: http://www.atsdr.cdc.gov/HAC/PHA/libby/lib_toc.html.

ATSDR (Agency for Toxic Substances and Disease Registry) (2001) Toxicological profile for asbestos. Atlanta GA. Available at http://www.atsdr.cdc.gov/toxprofiles/tp61.html.

ATSDR (2002a) Preliminary findings of Libby, Montana asbestos medical testing (combined testing 2000 and 2001). Atlanta, GA: Agency for Toxic Substances and Disease Registry.

ATSDR (2002b) Mortality in Libby, Montana, 1979-1998. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Anderson, H; Lilis, R; Daum, S; et al. (1979) Household exposure to asbestos and risk of subsequent disease, pp 145-156, in Dusts and Disease: Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dust and Their Extension into the Environment, R Lemen and J Dement, eds. Society for Occupational and Environmental Health. Pathotox Publishers, Park Forest South, Illinois.

Becklake, MR (1994) Symptoms and pulmonary functions as measures of morbidity. Ann Occup Hyg 38:569-580.

Case, BW; Dufresne, A; McDonald, AD; et al.(2000) Asbestos fiber type and length in lungs of chrysotile textile and production workers; Fibers longer than 18 µm. Inhal Toxicol 12:411-418.

Castellan, RM; Sanderson, WY; and Peterson, MR (1985) Prevalence of radiographic appearance of pneumoconiosis in an unexposed blue collar population. Am Rev Respir Dis 131:684-686.

Coin, PG; Roggli, VL; and Brody, AR (1994) Persistence of long, thin chrysotile asbestos fibers in the lungs of rats. Environ Health Perspect 102, supplement 5:197-199.

Cotran, RS; Kumar, V; and Collins, T (1999) Robbins pathologic basis of disease, 6th ed. 732-734. Philadelphia, WB Saunders Company.

Cugell, DW; and Kamp, DW (2004) Asbestos and the pleura: a review. Chest 125:1103-1117.

Dodson, RF; O'Sullivan, MF; Brooks, DR; et al. (2001) Asbestos content of omentum and mesentery in non-occupationally exposed individuals. Toxicol Ind Health 17:138-143.

Finkelstein, MM; and Dufresne, A (1999) Inferences on the kinetics of asbestos deposition and clearance among chrysotile miners and millers. Am J Ind Med 35:401-412.

Griffis, LC; Pickrell, JA; Carpenter, RL; et al. (1983) Deposition of crocidolite asbestos and glass microfibers inhaled by the Beagle dog. J Am Ind Hyg Assoc 44:216-222.

Hansen, J; de Klerk, NH; Musk, AW; et al. (1998) Environmental exposure to crocidolite and mesothelioma, exposure-response relationships. Am J Respir Crit Care Med 157:69-75.

Harris, RL jr; and Fraser DA (1976) A model for deposition of fibers in the human respiratory system. J Am Ind Hyg Assoc 37:73-89.

Harris, RL jr; and Trimbrell, V (1975) The influence of ffibre shape in lung deposition – mathematical estimates. Inhaled Part 4:75-89.

Hillerdal, G (1994) The human evidence: parenchymal and pleural changes. Ann Occup Hyg 38:561-567.

Jones, AD; McMillan, CH; Johnston, AM; et al. (1988) Pulmonary clearance of UICC amosite fibers inhaled by rats during chronic exposure at low concentration. Br J Ind Med 45:300-304.

International Labour Organization (ILO) (2000) Guidelines for the use of ILO international classification of radiographs of pneumoconiosis. Revised edition, 2000. International Labour Office, Geneva, Switzerland.

Lockey, JE (1985) Pulmonary hazards associated with vermiculite exposure. MS Thesis, University of Cincinnati.

Lockey, JE; Brooks, SM; Jarabek, AM; et al. (1984) Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis 129: 952-958.

Lockey et al. (2006) Personal communication to Robert Benson, EPA Region 8.

McDonald, JC; Harris, J; Armstrong, B (2004) Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. Occup Environ Med 61:363-366.

McDonald, JC; McDonald, AD; Armstrong, B; et al. (1986a) Cohort study of mortality of vermiculite miners exposed to tremolite. Brit J Ind Med 43:436-444.

McDonald, JC; Sebastien, P; and Armstrong, B (1986b) Radiological survey of past and present vermiculite miners exposed to tremolite. Brit J Ind Med 43:445-449.

Meeker, GP; Bern, AM; Brownfield, HA; et al. (2003) The composition and morphology from the Rainy Creek complex, near Libby, Montana. American Mineralogist 88:1955-1969.

Muravov, OI; Kaye, WE; Lewin, M; et al. (2005) The usefulness of computed tomography in detecting asbestos-related pleural abnormalities in people who had indeterminate chest radiographs: the Libby, MT, experience. Int J Hyg Environ Health 208:87-99.

Myoto, T; and Takaya, M (2001) Estimation of fibrous aerosol deposition in upper bronchi based on experimental data with model bifurcation. Ind Health 39:141-149.

Noonan, CW; Pfau, JC; Larson, TC; et al. (2006) Nested case-control study of autoimmune disease in an asbestos-exposed population. Environ Health Perspect 114:1243-1247.

NRC (National Research Council) (1983) Risk assessment in the federal government: managing the process. Washington, DC: National Academy Press.

Peipins, LC; Lewin, M; Campolucci, S; et al. (2003) Radiographic abnormalities and exposure to asbestos-contaminated vermiculite in the community of Libby, Montana, USA. Environ Health Perspect 111:1753-1759.

Pfau, JC; Sentissi, JJ; Weller, G; et al. (2005) Assessment of autoimmune responses associated with asbestos exposure in Libby, Montana, USA. Environ Health Perspect 113:25-30.

Rosenstock, L; and Hudson, LD (1987) The pleural manifestations of asbestos exposure. Occup Med 2:383-407.

Rudd, RM (1996) New developments in asbestos-related pleural disease. Thorax 51:210-216.

Solomon, A (1991) Radiological features of asbestos-related visceral pleural changes. Am J Ind Med 19:339-355.

Srebro, SH and Roggli, VL (1994) Asbestos-related disease associated with exposure to asbestiform tremolite. Am J Ind Med 26:809-819.

Terra-Filho, M; Kavakama, J; Bagatin, E; et al. (2003) Identification of rounded atelectasis in workers exposed to asbestos by contrast helical computed tomography.

Tossavainen, A; Karjalainen, A; and Karhunen, PJ (1994) Retention of asbestos fibers in the human body. Environ Health Perspect 102, supplement 5:253-255.

U.S. EPA (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington, DC; EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB2000-500023, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (1995) Use of the benchmark dose approach in health risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-94/007. Available from: National Technical Information Service, Springfield, VA; PB95-213765, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (2000) Benchmark dose technical guidance document [external review draft]. Risk Assessment Forum, Washington, DC; EPA/630/R-00/001. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (2006) Science policy council handbook: peer review. 3nd edition. Office of Science Policy, Office of Research and Development, Washington, DC; EPA/100/B-06/002. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

Wagner, JC; Berry, G; Skidmore, JW; et al. (1974) The effects of the inhalation of asbestos in rats. Br J Cancer 29:252-269.

Whitehouse, AC (2004) Asbestos-related pleural disease due to tremolite associated with progressive loss of lung function: serial observations in 123 miners, family members, and residents of Libby, Montana. Amer J Ind Hyg 46:219-225.

Witschi, HR; and Last, JA (1996) In Casarett and Doull's Toxicology: The Basic Science of Poisons, Fifth Edition. Klassen CD, editor. McGraw-Hill Companies, Inc.

Wright, R; Abraham, JL; Harber, P; et al. (2002) Fatal asbestosis 50 years after brief high intensity exposure in a vermiculite expansion plant. Am J Respir Crit Care Med 165:1145-1149.

APPENDIX A. SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

To be added.

APPENDIX B. BENCHMARK DOSE CALCULATIONS

Calculations using Cumulative Exposure (fibers-yr/cc)

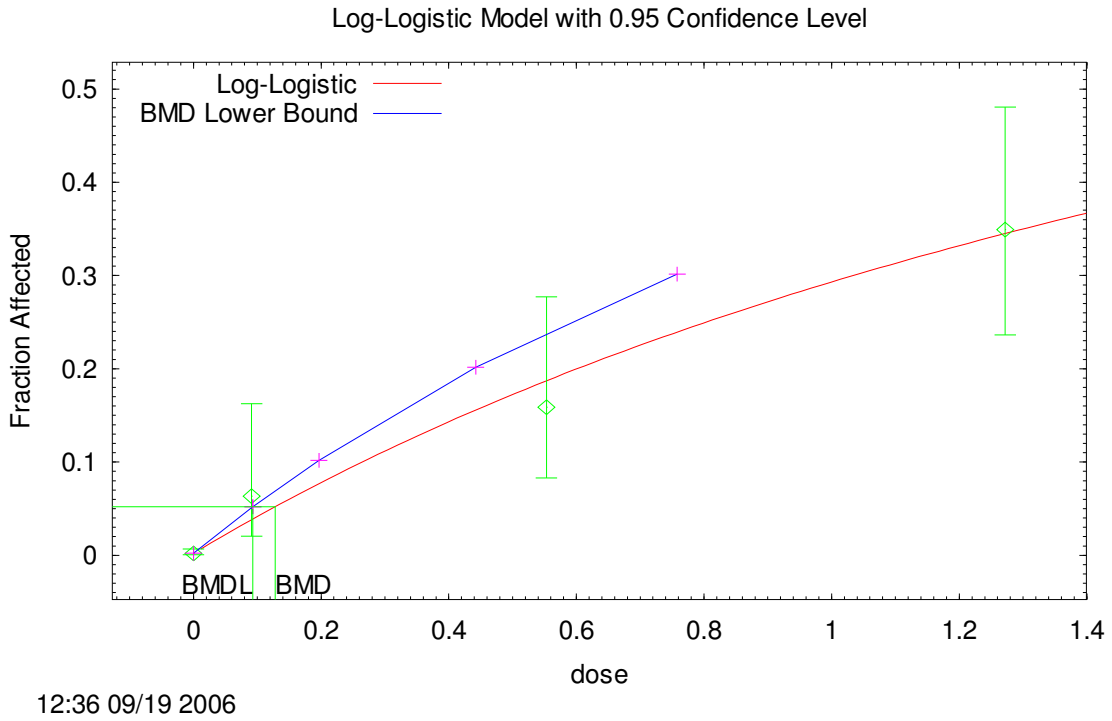
The data from Table 4-4 (workers with no previous exposure to asbestos) showing discrete pleural thickening or discrete pleural thickening plus diffuse pleural thickening were analyzed using benchmark dose methodology (EPA, 1995). These data were used to avoid any bias from non-quantified previous exposure to asbestos. Because of the wide range of exposures in each quartile, especially in the upper quartile, the median exposure was used within each exposure quartile. None of the models provided a satisfactory fit using all the exposure quartiles. The data were then analyzed excluding the highest exposure quartile and adding the background data (3/1422) from Castellan et al. (1985). Because the exposure-response relationship at the lower exposures is of greatest interest, this is an acceptable approach using the benchmark dose methodology (U.S. EPA, 2000, 1995). The results for discrete pleural thickening only are summarized in the table below. The Log-Logistic model provides the best fit based on a combination of visual fit, P value (P >0.1, and AIC (lowest value). When the background value (2/326) from Anderson et al. (1979) was used, the $BMCL_{05}$ with the Log-Logistic model was 0.0952311. When no background was used, the $BMCL_{05}$ with the Log-Logistic model was 0.101312.

Model	**P value**	**AIC**	**BMC_{05}**	**$BMCL_{05}$**
Gamma	0.374	215	0.148243	0.113493
Logistic	0.0000	239.97	0.597347	0.525179
Log-Logistic	**0.4867**	**214.682**	**0.127907**	**0.0931002**
Multistage	0.374	215	0.148243	0.113493
Probit	0.0000	234.618	0.513345	0.447231
Log-Probit	0.0000	227.773	0.313745	0.252167
Quantal Linear	0.374	215	0.148243	0.113493
Quantal Quadratic	0.0000	229.229	0.394452	0.342546
Weibull	0.374	215	0.148243	0.113493

The detailed results of the Log-Logistic model with the background values from Castellan et al. (1985) are included below.

```
 ================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: C:\BMDS\DATA\AMYSETDISCRETEPLUS.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\AMYSETDISCRETEPLUS.plt
                                      Tue Sep 19 12:36:58 2006
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

The form of the probability function is:
      P[response] = background+(1-background)/[1+EXP(-intercept-
      slope*Log(dose))]
```

```
Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial Parameter Values
Background =  0.0021097
Intercept  = -0.873244
Slope      =  1

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -slope have been estimated at a boundary
point, or have been specified by the user,and do not appear in the
correlation matrix.)

             Background    Intercept
Background   1             -0.044
Intercept   -0.044          1

Parameter Estimates
     Variable           Estimate             Std. Err.
     Background         0.00215981           0.0012442
     Intercept         -0.887989             0.198129
     Slope              1                    NA

NA - Indicates that this parameter has hit a bound implied by some
inequality constraint and thus has no standard error.

Analysis of Deviance Table
  Model            Log(likelihood)  Deviance  Test DF     P-value
  Full model       -104.702
  Fitted model     -105.341           1.27705  2          0.5281
  Reduced model    -183.645         157.885    3          <.0001
           AIC:          214.682

Goodness of Fit
                                                                  Scaled
Dose        Est._Prob.     Expected       Observed   Size      Residual
-------------------------------------------------------------------------
0.0000      0.0022          3.071          3         1422      -0.0407
0.0910      0.0382          2.405          4           63       1.049
0.5530      0.1871         11.789         10           63      -0.5779
1.2720      0.3450         21.735         22           63       0.07034

 Chi-square = 1.44     DF = 2        P-value = 0.4867

Benchmark Dose Computation
Specified effect = 0.05
Risk Type        = Extra risk
Confidence level = 0.95
             BMD = 0.127907
            BMDL = 0.0931002
```



To try to establish more clearly the exposure-response relationship in the low exposure region, EPA redefined the data set into groups of 25 individuals (26 if the last two individuals in the group had the identical exposure) for those with no previous exposure to asbestos from the data supplied by the UC Research Group. These data are summarized in the table below. Only the median exposure in each group is listed.

Exposure (fibers-year/cc)	**Prevalence of Pleural Thickening**		
	Discrete	**Diffuse**	**Discrete plus Diffuse**
0.045	1/25	0/25	1/25
0.121	2/25	0/25	2/25
0.276	1/25	0/25	1/25
0.489	6/25	0/25	6/25
0.725	4/25	0/25	4/25
1.081	8/25	0/25	8/25
1.475	10/26	0/26	10/26
2.414	8/25	1/25	9/25
4.301	7/25	4/25	11/25
16.252	9/26	5/25	14/26
Total	56/252	10/252	66/252

The data were analyzed using the incidence of discrete pleural thickening or discrete plus diffuse pleural thickening. None of the models gave a satisfactory fit when all of the data were included. Therefore, the data were re-analyzed dropping the highest exposure group until a satisfactory fit was obtained. This occurred when the top three

exposure groups were excluded. As there were no cases of diffuse pleural thickening in that exposure range, the analysis of discrete plus diffuse pleural thickening was not conducted. A summary of the calculations for discrete pleural thickening including the background values (3/1422) from Castellan et al. (1985) follows. The Log-Logistic model provides the best fit based on a combination of visual fit, P value (P >0.1, and AIC (lowest value). When the background value (2/326) from Anderson et al. (1979) was used, the $BMCL_{05}$ with the Log-Logistic model was 0.093599. When no background value was included, the $BMCL_{05}$ with the Log-Logistic model was 0.0952139. The point of departure used to derive the RfC will be the same regardless of which of these values is used.

Model	**P value**	**AIC**	**BMC_{05}**	**$BMCL_{05}$**
Gamma	0.6396	197.266	0.147697	0.111331
Logistic	0.0000	225.471	0.603725	0.525878
Log-Logistic	**0.7165**	**197.027**	**0.127996**	**0.0915492**
Multistage	0.6396	197.266	0.14769	0.111331
Probit	0.0000	218.502	0.517721	0.44794
Log-Probit	0.0000	206.698	0.299958	0.241397
Quantal Linear	0.6396	197.266	0.147696	0.111331
Quantal Quadratic	0.0000	210.365	0.38919	0.335685
Weibull	0.6396	197.266	0.147696	0.111331

The detailed results of the Log-Logistic model with the background values from Castellan et al. (1985) are included below.

```
 ================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: C: \BMDS\DATA\ASBNOPREVPLUSC.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\ASBNOPREVPLUSC.plt
                                          Thu Aug 03 08:17:29 2006
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

The form of the probability function is:
      P[response] = background+(1-background)/[1+EXP(-intercept-
      slope*Log(dose))]
Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 8
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model
```

Default Initial Parameter Values
Background = 0.0021097
Intercept = -0.996185
Slope = 1

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s)-slope have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix.)

	Background	intercept
Background	1	-0.043
Intercept	-0.043	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.00215264	0.00123877
Intercept	-0.888451	0.209376
Slope	1	NA

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

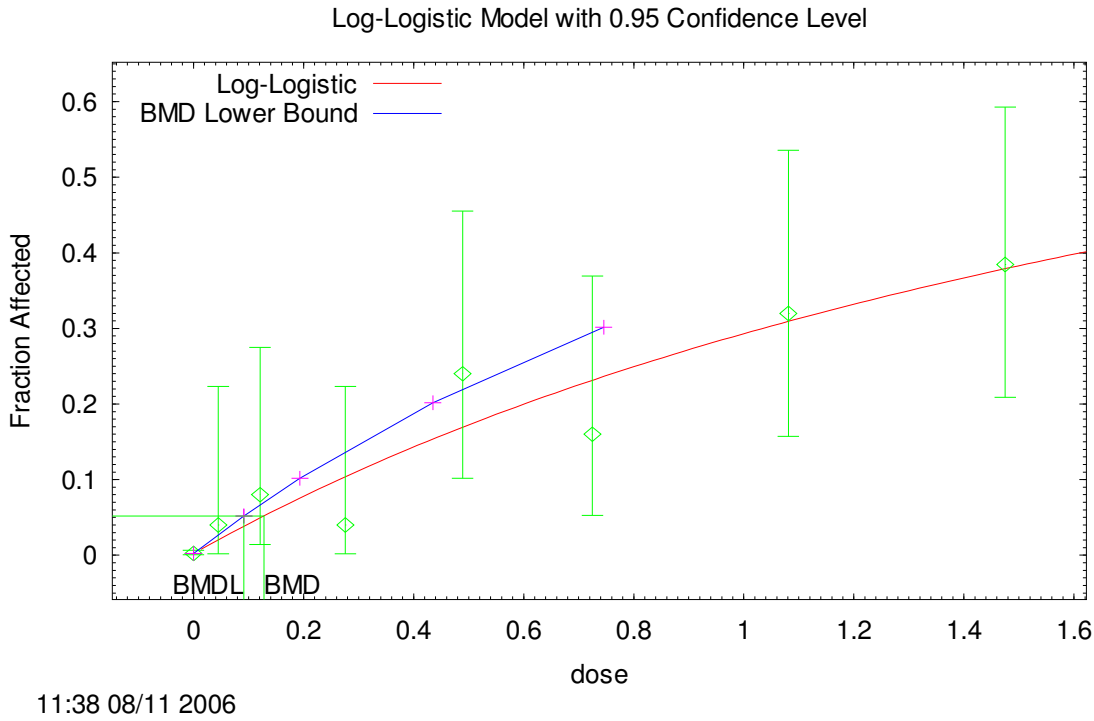
Model	Log (likelihood)	Deviance	Test DF	P-value
Full model	-94.6106			
Fitted model	-96.5133	3.80541	6	0.703
Reduced model	-168.354	147.488	7	<.0001
AIC:	197.027			

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0022	3.061	3	1422	-0.03493
0.0450	0.0203	0.507	1	25	0.6992
0.1210	0.0495	1.236	2	25	0.7043
0.2760	0.1039	2.597	1	25	-1.047
0.4890	0.1692	4.231	6	25	0.9436
0.7250	0.2314	5.785	4	25	-0.8464
1.0810	0.3093	7.732	8	25	0.1162
1.4740	0.3789	9.852	10	26	0.05977

Chi-square = 3.71 DF = 6 P-value = 0.7165

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.127966
BMDL = 0.0915492



Calculation of the Human Equivalent Concentration from the $BMCL_{05}$

The $BMCL_{05}$ calculated above must be converted to a Human Equivalent Concentration for continuous exposure (that is 7 days per week and 24 hours per day). EPA's 1994 Inhalation Dosimetry guidance (EPA, 1994) recommends adjusting data from an occupation study using the assumption that exposure occurs 5 days per week and that the worker breathes 10 m^3 during an 8-hour work shift and 20m^3 in a 24 hour day. Using this procedure, the adjustment factor is (5/7 x 10/20) and the human equivalent concentration would be $BMCL_{05}$ x 5/7 x 10/20.

There is uncertainty about the actual work shift in the facility. The UC researchers assumed that each individual worked each calendar day in the year. It is known that during the winter and early spring the individuals worked more than an 8 hour shift and more than 5 days per week. The individuals worked a more normal work shift the remainder of the year. Unfortunately, work histories to the needed level of precision are not available. Therefore, it is uncertain whether the correction for the number of days worked per week should be 5/7, 6/7, or 7/7. It is also uncertain how to adjust the assumption that a worker breathes 10 m^3 during an 8-hour work shift to the actual hours per day worked for each individual. For example, assuming a linear correction, a worker would breathe 15 m^3 for a 12-hour work shift and 12.5m^3 for a 10-hour work shift. EPA assumed that a reasonable range of actual work shifts, would include:

1) 6 months at 10 hrs/day, 6 days/wk, and 6 months at 8 hrs/day, 5 days/wk
2) 4 months at 12 hrs/day, 6 days/wk, and 8 months at 8 hrs/day, 5 days/wk
3) 12 months at 8 hrs/day, 7 days/wk

4) 12 months at 8 hrs/day, 6 days/wk
5) 12 months at 8 hrs/day, 5 days/wk

Of these possibilities, EPA made the judgment that scenarios 1, 2, and 4 were the most probable and scenarios 3 and 5 were the least probable. In the absence of any firm guidance on how to choose a preferred value, EPA decided to use a correction factor derived from the geometric mean of scenarios 1, 2, and 4 (0.442344) in this assessment. If the full range of scenarios were used, the geometric mean for the correction factor would be 0.434382. Therefore, the point of departure used to calculate the RfC is 0.04 fibers-year/cc (0.0915492 x 0.442344 = 0.0404962, rounded to 0.04).

Calculations using Concentration Only (fibers/cc)

For some applications of the RfC for LA, it is useful to have the exposure in concentration units only (fibers/cc). To facilitate that analysis, EPA conducted the benchmark dose analysis from the data in the following table. This table was constructed from the data supplied by the UC Research Team by dividing cumulative exposure (fibers-yr/cc) by the duration of exposure (years of exposure) for each individual in the study.

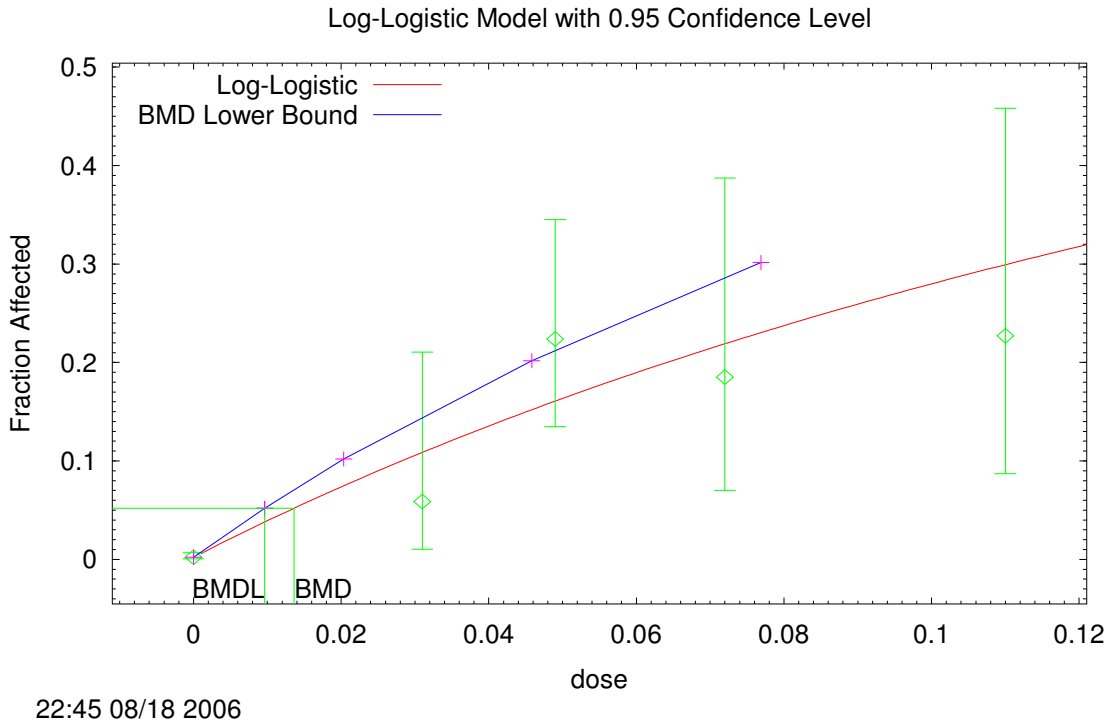
Exposure (fibers/cc)	**Incidence of Pleural Thickening**	
	Discrete	**Discrete plus Diffuse**
0.031- <0.049 (median 0.031)	2/34	2/34
0.049	15/67	15/67
0.50 – <0.11 (median 0.072)	5/27	5/27
0.11	5/22	6/22
>0.11 – 0.201 (median 0.146)	6/35	7/35
0.202 – 0.440 (median 0.297)	14/35	17/35
0.470 – 1.200 (median 0.843)	9/32	14/32
Total	56/252	66/252

None of the models gave a satisfactory fit when all of the data were used. A satisfactory fit was obtained when the top three exposures were excluded. A summary of the calculations for discrete pleural thickening including the background value (3/1422) from Castellan et al. (1985) follows. The Log-Logistic model provides the best fit based on a combination of visual fit, P value (P >0.1, and AIC (lowest value). The detailed results of the Log-Logistic model are included below. A slightly lower value for the $BMCL_{05}$ (0.00939746) was obtained with the Log-Logistic model when the background value (2/326) from Anderson et al. (1979) was used. When no background value was included, the $BMCL_{05}$ for the Log-Logistic model was again slightly lower (0.0095741). The point of departure used to derive the RfC will be the same regardless of which of these values is used.

Model	P value	AIC	BMC_{05}	$BMCL_{05}$
Gamma	0.2594	186.851	0.0150053	0.0110667
Logistic	0.0000	217.169	0.047705	0.0413915
Log-Logistic	**0.3111**	**186.486**	**0.0136236**	**0.00964542**
Multistage	0.2594	186.851	0.0150057	0.0110667
Probit	0.0000	207.588	0.0415565	0.0359253
Log-Probit	0.0821	189.455	0.0274197	0.0224424
Quantal Linear	0.2594	186.851	0.0150057	0.0110667
Quantal Quadratic	0.0051	194.538	0.0320874	0.027531
Weibull	0.2594	186.851	0.0150057	0.0110667

```
 ================================================================
        Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
        Input Data File: C:\BMDS\ASBESTOSCONC.(d)
        Gnuplot Plotting File:  C:\BMDS\ASBESTOSCONC.plt
                                        Fri Aug 18 22:45:14 2006
 ================================================================
 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
The form of the probability function is:
   P [response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is restricted as slope >= 1
Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
User has chosen the log transformed model

Default Initial Parameter Values
      Background  = 0.0021097
      Intercept   = 1.41433
      Slope       = 1.09862

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s)-slope have been estimated at a boundary
point, or have been specified by the user, and do not appear in the
correlation matrix.)
                  background        intercept
      background   1                -0.033
      intercept   -0.033             1

Parameter Estimates
      Variable    Estimate    Std. Err.
      background  0.00211128  0.00121726
      intercept   1.35151     0.217525
      slope       1           NA

      NA - Indicates that this parameter has hit a bound implied by
      some inequality constraint and thus has no standard error.
```

```
Analysis of Deviance Table
      Model              Log (likelihood)  Deviance    Test DF     P-
value
      Full model          -89.4444
      Fitted model        -91.2428           3.59682   3
      0.3084
      Reduced model      -148.479          118.069     4
      <.0001
            AIC:          186.486

Goodness of Fit
                                                          Scaled
Dose        Est._Prob.  Expected    Observed    Size    Residual
-----------------------------------------------------------------------
0.0000      0.0021       3.002       3          1422   -0.001295
0.0310      0.1088       3.700       2            34   -0.9364
0.0490      0.1609      10.783      15            67    1.402
0.0720      0.2193       5.920       5            27   -0.4281
0.1100      0.2997       6.594       5            22   -0.7416
      Chi-square = 3.58        DF = 3      P-value = 0.3111

Benchmark Dose Computation
      Specified effect   = 0.05
      Risk Type          = Extra risk
      Confidence level   = 0.95
      BMD                = 0.0136236
      BMDL               = 0.00964542
```



Calculation of the Human Equivalent Concentration from the $BMCL_{05}$

As noted above, there is uncertainty regarding the correction factor for calculating the human equivalent concentration. As above, the geometric mean of the correction factor derived from the three most probable work scenarios (0.442344) is used to derive the point of departure from the $BMCL_{05}$ of 0.00964542**.** Therefore, the point of departure used to calculate the RfC is 0.004 fibers/cc (0.00964542 x 0.442344 = 0.0042665, rounded to 0.004).